Appln No.: 09/786,502
Amendment Dated: May 11, 2005
Reply to Office Action of February 11, 2005

REMARKS/ARGUMENTS

This is in response to the Office Action mailed February 11, 2005 for the above-captioned application. Reconsideration and further examination are respectfully requested.

Claims 1-6, 12, 13, 16-20 and 25-32 were examined. The limitation of claim 6 has been added to claim 1, and claims 6 and 17-20 which recited this limitation have been canceled. Claims 7-11 and 21-24 are withdrawn from consideration.

The Examiner rejected claims 1-3, 12, 13, 25, 26, 29 and 30 under 35 USC § 103 as obvious over Eshhar in view of Murphy I and Murphy II. This rejection is rendered moot by the amendment of claim 1 to include the limitation of claim 6 which was not subject to this rejection.

The Examiner rejected claims 1-3, 12, 29 and 30 under 35 USC § 103 as obvious over Capon in view of Murphy I and Murphy II. This rejection is rendered moot by the amendment of claim 1 to include the limitation of claim 6 which was not subject to this rejection.

The Examiner rejected claims 13 and 16 under 35 USC § 103 as obvious over Eshhar or Capon in view of Murphy I and Murphy II and Gallardo. This rejection is rendered moot by the amendment of claim 1 to include the limitation of claim 6 which was not subject to this rejection.

The Examiner rejected claims 4, 19, 27 and 31 under 35 USC § 112, first paragraph, for failure to comply with the written description requirement. Without conceding the correctness of this rejection, claims 4, 19, 27 and 31 have been canceled.

Claims 1-3, 5, 6, 12, 13, 17, 18, 19, 25, 26, 28, 29, 30, 32 are rejected under 35 USC § 103 over Eshhar or Capon, in view of Murphy I, Murphy II, and Moritz. In these rejections, Moritz is cited as teaching a CD8 connector, and the Examiner argues that it would have been prima facie obvious to pick this connector to use with a PSMA specific scFv and a cytoplasmic domain. In support of this contention, the Examiner argues that "it appears that the prior art recognized the need for a spacer region and the particular nature of the spacer region is not important." (Office Action, Page 12). Applicants respectfully traverse this rejection.

Applicants once again assert that this rejection is founded on hindsight. The U.S. Court of Appeals for the Federal Circuit has stated that "[t]he mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification." *In re Fritch*, 972 F.2d 1260, 1266, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992) (citing *In re Gordon*, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984)). Although this statement is couched in terms of modifying the prior art, it is equally applicable to combining teachings found in the prior art. Specifically,

the mere fact that teachings found in the prior art could be combined as proposed by an examiner does not make the combination obvious "absent some teaching, suggestion or incentive supporting the combination." *Carella v. Starlight Archery and Pro Line Co.*, 804 F.2d 135, 140, 231 USPQ 644, 647 (Fed. Cir. 1986) (citing *ACS Hosp. Syss., Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984)).

In the present application, the claims are directed to fusion protein compositions that comprise an scFv that binds to PSMA connected, via a CD8 connector, to the cytoplasmic domain of a molecule that functions as a transducer of a mammalian immune response in the presence of a costimulatory factor. The art takes each of these limitations, in isolation. Further, the art is selected from among myriad references that relate to other cytoplasmic domains, to other connectors, and to other scFv's to arrive at the precise combinations of the claims. There is no suggestion in any reference to choose these specific components, however. Thus, the rejection is based entirely on the guidance of the present invention.

Looking first at claim 1, the claim recites fusion receptor composition which is a construct of a PSMA-scFv, a CD 8 connector and a cytoplasmic domain. The cytoplasmic domain is one that functions as a transducer of a mammalian immune response in the presence of a costimulatory factor, and the fusion receptor as a whole is effective to promote a cellular immune response to PSMA. The Examiner takes the position that the primary reference, Eshhar, teaches every limitation of this claim except for the specific choice of PSMA as the antigen to which the scFv is targeted. She then argues that PSMA is a known antigen and that making a fusion preceptor with the scFv for PSMA would therefore have been obvious. Implicit in this argument is the broader argument that the disclosure of Eshhar and Capon are effective to render any fusion receptor of a known scFv and a cytoplasmic domain obvious.

When one looks at the actual scope of the Examiner's argument, it bears a striking resemblance to rejections that have been deemed improper because they represent so-called obvious-to-try type of rejections. The Federal Circuit in *In re O'Farrell*, 7 USPQ2d 1673, 1681 (Fed Cir. 1988) observed that "the admonition that 'obvious to try' is not the standard under § 103 has been directed mainly at two kinds of error." This case is one of the second type, namely a case in which it may have been obvious "to explore a new technology or general approach that seemed to be a promising field of experimentation, where the art gave only general guidance as to the particular form of the claimed invention, or how to achieve it." *Id.* at 1681. A statement of general applicability, particularly in a patent disclosure as the examiner asserts is present in Eshhar, does not overcome the basic knowledge in the art, and is still nothing more than .

With respect to the specific recitation of the incorporation of a CD8 hinge section as the connector, the Examiner cites a reference which uses a different scFv from the claimed

invention, a γ receptor domain and a CD8 hinge. The Examiner's entire argument is that because the CD8 hinge is used in this molecule, putting it in any other fusion, including that now being claimed would have been obvious. The Examiner has not, however, pointed to any suggestion in the references that the CD8 hinge is of such general applicability, nor explained why such applicability would be expected based on what is taught. Thus, the Examiner has merely found the pieces of the claimed invention in the art and has not made the connections required to support an obviousness rejection. See, *Ex Parte Hiyamizu*, 10 USPQ 2d 1393, 1394 (POBAI 1988)("Citing references which merely indicate the isolated elements ... are known is not a sufficient basis for concluding that the combination of elements would have been obvious.").

As further evidence of patentability, Applicants enclose a copy of a recent publication that contradicts the Examiner's assertion that the nature of the connector is unimportant. This paper shows that the combination of the spacer or connector and the scFv are important to the activity of the type of construct now claimed. Nothing in the art suggests that the pairing of PSMA-scFv and CD connector would be a correct choice.

Finally, Applicants submit that the Examiner has filed to properly take into account the characteristics of the claimed fusion proteins in assessing obviousness. As has been previously pointed out, biotechnology is a complex art, and the ability to make a given construct and the functional properties of that construct cannot be said to be generally predictable. In determining obviousness, however, the properties that are disclosed for the constructs of the art and the constructs of the invention must be taken into account, and any differences between these properties is fair evidence of unobviousness. *See, In re Margolis*, 228 U.S.P.Q. 940 (Fed. Cir. 1986).

As noted in the present application, tests showing IL-2 stimulation, while suggestive of utility, are not dispositive since they may be followed by T cell anergy or apoptosis. This results in T cell death *in vivo* rather than the development of an appropriate immune response. (Page 3, lines 31-33; Page 14, lines 47) Insufficient costimulatory signals and perhaps other problems can render a composition effectively useless if the cells expressing the fusion does not remain alive, undergo proliferation and respond when a restimulation occurs. Eshhar, however, does not demonstrate such activity, and art such as the Alternschmidt article (cited on Page 14 of the present application) show that it may not be presumed for different antibodies than the one tested in Eshhar. In contrast, the present application does demonstrate this activity for PSMA-CD8 containing species. This is a patentable and unobvious advance over the art which teaches at best techniques, and not the claimed invention.

In Paragraphs 18-20 of the Official Action, the Examiner presented further rejections under 35 USC § 103. These rejections are not applied to claim 6, and therefore are moot in view of the amendment of claim 1 to include the recitation of the CD8 connector.

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Claims 3 and 26 were provisionally rejected for obviousness-type double patenting. This rejection is not applied to claim 6, and therefore is moot in view of the amendment of claim 1 to include the recitation of the CD8 connector.

For these reasons, the elected claims are believed to be in form for allowance. Accordingly, recombination of the withdrawn claims related to unelected species and methods of using the fusion proteins and allowance of the application as a whole is hereby requested.

Respectfully Submitted,

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Attachment

Guest et al., J. Immunotherapy 28: 203-211 (2005).